

ACC/AHA Practice Guideline

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult—Summary Article

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)

Developed in Collaboration With
the American College of Chest Physicians and the International
Society for Heart and Lung Transplantation

Endorsed by the Heart Rhythm Society

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I. Introduction

The American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines regularly reviews existing guidelines to determine when an update or full revision is needed. This process gives priority to areas where major changes in text, particularly recommendations, are required on the basis of new understanding of evidence. Minor changes in verbiage and references are discouraged. The ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult published in 2001 have now been updated. The full-text guidelines incorporating the updated material are e-published in the *Journal of the American College of Cardiology* and *Circulation* on the ACC Web site (www.acc.org) and the AHA Web site (www.americanheart.org) in 2 versions: a version highlighting the changes in recommendations (i.e., deleted text struck through, new text underlined) from the 2001 guideline to the 2005 guideline and a “clean” version that incorporates all

changes in the recommendations. (The “track change” version only highlights changes to the recommendations; it does not show changes to supporting text, tables, or figures.) This article describes the major areas of change reflected in the update. Please note we have changed the Table of Contents headings in the 2001 guidelines from roman numerals to unique identifying numbers. Interested readers are referred to the full-text guideline to completely understand the context of these changes.

Heart failure (HF) is a major and growing public health problem in the United States. Approximately 5 million patients in this country have HF, and more than 550 000 patients are diagnosed with HF for the first time each year (1). The disorder is the primary reason for 12 to 15 million office visits and 6.5 million hospital days each year (2). From 1990 to 1999, the annual number of hospitalizations has increased from approximately 810 000 to over 1 million for HF as a

primary diagnosis and from 2.4 to 3.6 million for HF as a primary or secondary diagnosis (3). In 2001, nearly 53 000 patients died of HF as a primary cause. The number of HF deaths has increased steadily despite advances in treatment, in part because of increasing numbers of patients with HF due to better treatment and “salvage” of patients with acute myocardial infarctions (MIs) earlier in life (1).

Heart failure is primarily a condition of the elderly (4), and thus the widely recognized “aging of the population” also contributes to the increasing incidence of HF. The incidence of HF approaches 10 per 1000 population after age 65 (1) and approximately 80% of patients hospitalized with HF are more than 65 years old (5). Heart failure is the most common Medicare diagnosis-related group (i.e., hospital discharge diagnosis), and more Medicare dollars are spent for the diagnosis and treatment of HF than for any other diagnosis (6). It has been estimated that in 2005, the total direct and indirect cost of HF in the U.S. will be equal to \$27.9 billion (1). In the United States, approximately \$2.9 billion annually is spent on drugs for the treatment of HF (1).

The ACC and the AHA first published guidelines for the evaluation and management of HF in 1995 (7) and published revised guidelines in 2001 (8). Since that time, a great deal of progress has been made in the development of both pharmacological and nonpharmacological approaches to treatment for this common, costly, disabling, and potentially fatal disorder. Available treatments have increased, but this increase has rendered clinical decision making far more complex. The timing and sequence of initiating treatments and the appropriateness of prescribing them in combination are uncertain. The increasing recognition of the existence of clinical HF in patients with a normal ejection fraction (EF) has also led to heightened awareness of the limitations of evidence-based therapy for this important group of patients. For these reasons, the 2 organizations believed that it was appropriate to reassess and update these guidelines, fully recognizing that the optimal therapy of HF remains a work in progress and that future advances will require that the guideline be updated again.

In formulating the 2001 document, the writing committee decided to take a new approach to the classification of HF, one that emphasized both the development and progression of the disease. In doing so, the 2001 document identified 4 stages involved in the development of the HF syndrome. The first 2 stages (A and B) are clearly not HF but are an attempt to help healthcare providers identify patients early who are at risk for developing HF. Stages A and B patients are best defined as those with risk factors that clearly predispose toward the development of HF. For example, patients with coronary artery disease, hypertension, or diabetes mellitus who do not yet demonstrate impaired left ventricular (LV) function, hypertrophy, or geometric chamber distortion would be considered Stage A, whereas patients who are asymptomatic but demonstrate LV hypertrophy (LVH) and/or impaired LV function would be designated as Stage B. Stage C then denotes patients with current or past symptoms of HF associated with underlying structural heart disease (the bulk of patients with HF), and Stage D designates patients with truly refractory HF who might be eligible for specialized,

advanced treatment strategies such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice.

This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions introduced even before the appearance of LV dysfunction or symptoms can reduce the population morbidity and mortality of HF. This classification system is intended to complement but in no way to replace the New York Heart Association (NYHA) functional classification, which primarily gauges the severity of symptoms in patients who are in Stage C or D. It has been recognized for many years that the NYHA functional classification reflects a subjective assessment by a healthcare provider and can change frequently over short periods of time. It has also been recognized that the treatments used may not differ significantly across the classes. Therefore, the committee believed that a staging system was needed that would reliably and objectively identify patients during the course of their developing disease and that would be linked to treatments uniquely appropriate at each stage of illness. According to this new staging approach, patients would only be expected to either not advance at all or to advance from one stage to the next, unless progression of the disease was slowed or stopped by treatment, and spontaneous reversal of this progression would be considered unusual. For instance, although symptoms (NYHA class) might vary widely over time (in response to therapy or to progression of disease) in a patient who has already developed the clinical syndrome of HF (Stage C), the patient could never return to Stage B (never had HF), and therapies recommended for Stage C will be appropriate even if this patient is in NYHA class I. This new classification scheme adds a useful dimension to our thinking about HF that is similar to that achieved by staging or risk assessment systems for other disorders (e.g., those used in the approach to cancer).

A classification of recommendation and level of evidence have been assigned to each recommendation. Classification of recommendations and levels of evidence are expressed in the ACC/AHA format as follows. Please refer to Table 1 in the full-text guidelines for more details.

Classification of Recommendations

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and/or effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure/therapy.

Ila: Weight of evidence/opinion is in favor of usefulness/efficacy.

Ilb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

Level of Evidence

Level of Evidence A: Data are derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B: Data are derived from a single randomized trial, or nonrandomized studies.

Level of Evidence C: Only consensus opinion of experts, case studies, or standard of care.

This document focuses on the prevention of HF and on the evaluation and management of chronic HF in the adult patient with normal or reduced LVEF. It specifically did not consider acute HF, which might merit a separate set of guidelines and is addressed in part in the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (9) and the ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non-ST Elevation Myocardial Infarction (10). We have also excluded HF in children, both because the underlying causes of HF in children differ from those in adults and because none of the controlled trials of treatments for HF have included children. We have not considered the management of HF due to primary valvular disease [see ACC/AHA Guidelines on the Management of Patients With Valvular Heart Disease (11)] or congenital malformations, and we have not included recommendations for the treatment of specific myocardial disorders (e.g., hemochromatosis, sarcoidosis, or amyloidosis).

The various therapeutic strategies described in this document can be viewed as a checklist to be considered for each patient in an attempt to individualize treatment for an evolving disease process. Every patient is unique, not only in terms of his or her cause and course of HF, but also in terms of his or her personal and cultural approach to the disease. Guidelines can only provide an outline for evidence-based decisions or recommendations for individual care; these guidelines are meant to provide that outline.

All of the recommendations in this guideline update were written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document, would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines. The rewritten recommendations appear under their respective headings.

Use of boldfaced type in the recommendations shows where the intent of the recommendations has changed from the 2001 guidelines.

II. Characterization of HF as a Clinical Syndrome

A. Definition of HF

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may

lead to pulmonary congestion and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema and report few symptoms of dyspnea or fatigue. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term "heart failure" is preferred over the older term "congestive heart failure."

The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, or great vessels, but the majority of patients with HF have symptoms due to an impairment of LV myocardial function. Heart failure may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved EF to those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, regardless of EF. Patients with normal EF may have a different natural history and may require different treatment strategies than patients with reduced EF, although such differences remain controversial (see Section 4.3.2 in the full-text guidelines).

Coronary artery disease, hypertension, and dilated cardiomyopathy are the causes of HF in a substantial proportion of patients in the Western world. As many as 30% of patients with dilated cardiomyopathy may have a genetic cause (12). Valvular heart disease is still a common cause of HF. In fact, nearly any form of heart disease may ultimately lead to the HF syndrome.

It should be emphasized that HF is not equivalent to cardiomyopathy or to LV dysfunction; these latter terms describe possible structural or functional reasons for the development of HF. Instead, HF is defined as a clinical syndrome that is characterized by specific symptoms (dyspnea and fatigue) in the medical history and signs (edema, rales) on the physical examination. There is no single diagnostic test for HF because it is largely a clinical diagnosis that is based on a careful history and physical examination.

B. Heart Failure as a Symptomatic Disorder

The approach that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the NYHA. This system assigns patients to 1 of 4 functional classes, depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels of exertion that would limit normal individuals (class I). Although the functional class tends to deteriorate over periods of time, most patients with HF do not typically show an uninterrupted and inexorable worsening of symptoms. Instead, the severity of symptoms characteristically fluctuates even in the absence of changes in medications, and changes in medications and diet can have either favorable or adverse effects on functional capacity in the absence of measurable changes in ventricular function. Some patients may demonstrate remarkable recovery, sometimes associated with improvement in structural and functional abnormalities. Usually, sustained improvement is

associated with drug therapy, and that therapy should be continued indefinitely.

The mechanisms responsible for the exercise intolerance of patients with chronic HF have not been defined clearly. Although HF is generally regarded as a hemodynamic disorder, many studies have indicated that there is a poor relation between measures of cardiac performance and the symptoms produced by the disease. Patients with a very low EF may be asymptomatic, whereas patients with preserved LVEF may have severe disability. The apparent discordance between EF and the degree of functional impairment is not well understood but may be explained in part by alterations in ventricular distensibility, valvular regurgitation, pericardial restraint, cardiac rhythm, conduction abnormalities, and right ventricular function (12). In addition, in ambulatory patients, many noncardiac factors may contribute substantially to exercise intolerance. These factors include but are not limited to changes in peripheral vascular function, skeletal muscle physiology, pulmonary dynamics, neurohormonal and reflex autonomic activity, and renal sodium handling. The existence of these noncardiac factors may explain why the hemodynamic improvement produced by therapeutic agents in patients with chronic HF may not be immediately or necessarily translated into clinical improvement. Although pharmacological interventions may produce rapid changes in hemodynamic variables, signs and symptoms may improve slowly over weeks or months or not at all.

C. Heart Failure as a Progressive Disorder

Left ventricular dysfunction begins with some injury to, or stress on, the myocardium and is generally a progressive process, even in the absence of a new identifiable insult to the heart. The principal manifestation of such progression is a change in the geometry and structure of the LV, such that the chamber dilates and/or hypertrophies and becomes more spherical—a process referred to as cardiac remodeling. This change in chamber size and structure not only increases the hemodynamic stresses on the walls of the failing heart and depresses its mechanical performance but may also increase regurgitant flow through the mitral valve. These effects, in turn, serve to sustain and exacerbate the remodeling process. Cardiac remodeling generally precedes the development of symptoms (occasionally by months or even years), continues after the appearance of symptoms, and contributes substantially to worsening of symptoms despite treatment. Progression of coronary artery disease, diabetes mellitus, hypertension, or the onset of atrial fibrillation may also contribute to the progression of HF. The development of structural abnormalities can have 1 of 3 outcomes: 1) patients die before developing symptoms (in stage A or B), 2) patients develop symptoms controlled by treatment, or 3) patients die of progressive HF. Sudden death can interrupt this course at any time.

Although several factors can accelerate the process of LV remodeling, there is substantial evidence that the activation of endogenous neurohormonal systems plays an important role in cardiac remodeling and thereby in the progression of HF. Patients with HF have elevated circulating or tissue levels of norepinephrine, angiotensin II, aldosterone, endothelin, vaso-

pressin, and cytokines, which can act (alone or in concert) to adversely affect the structure and function of the heart. These neurohormonal factors not only increase the hemodynamic stresses on the ventricle by causing sodium retention and peripheral vasoconstriction but may also exert direct toxic effects on cardiac cells and stimulate myocardial fibrosis, which can further alter the architecture and impair the performance of the failing heart. Neurohormonal activation also has direct deleterious effects on the myocytes and interstitium, altering the performance and phenotype of these cells.

The development of HF can be appropriately characterized by considering 4 stages of the disease, as described in the Introduction. This staging system recognizes that HF, like coronary artery disease, has established risk factors and structural prerequisites; that the development of HF has asymptomatic and symptomatic phases; and that specific treatments targeted at each stage can reduce the morbidity and mortality of HF (Figure 1).

Stages in the development of HF/recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; ACEI, angiotensin converting enzyme inhibitors; and ARB, angiotensin receptor blocker.

III. Initial and Serial Clinical Assessment of Patients Presenting With HF

In this section, recommendations for the evaluation of patients with HF have been separated into 2 sets of recommendations: 1) for the initial clinical assessment of patients presenting with HF and 2) for the serial clinical assessment of patients presenting with HF.

RECOMMENDATIONS FOR THE INITIAL CLINICAL ASSESSMENT OF PATIENTS PRESENTING WITH HEART FAILURE

CLASS I

1. A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders **or behaviors** that might cause or accelerate the development or progression of HF. (*Level of Evidence: C*)
2. **A careful history of current and past use of alcohol, illicit drugs, current or past standard or “alternative therapies,” and chemotherapy drugs should be obtained from patients presenting with HF.** (*Level of Evidence: C*)
3. In patients presenting with HF, initial assessment should be made of the patient’s ability to perform routine and desired activities of daily living. (*Level of Evidence: C*)
4. Initial examination of patients presenting with HF should include assessment of the patient’s volume status, **orthostatic blood pressure changes, measurement of weight and height, and calculation of body mass index.** (*Level of Evidence: C*)
5. Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, **fasting blood glucose (glycohemoglobin), lipid profile,** liver function tests, and thyroid-stimulating hormone. (*Level of Evidence: C*)

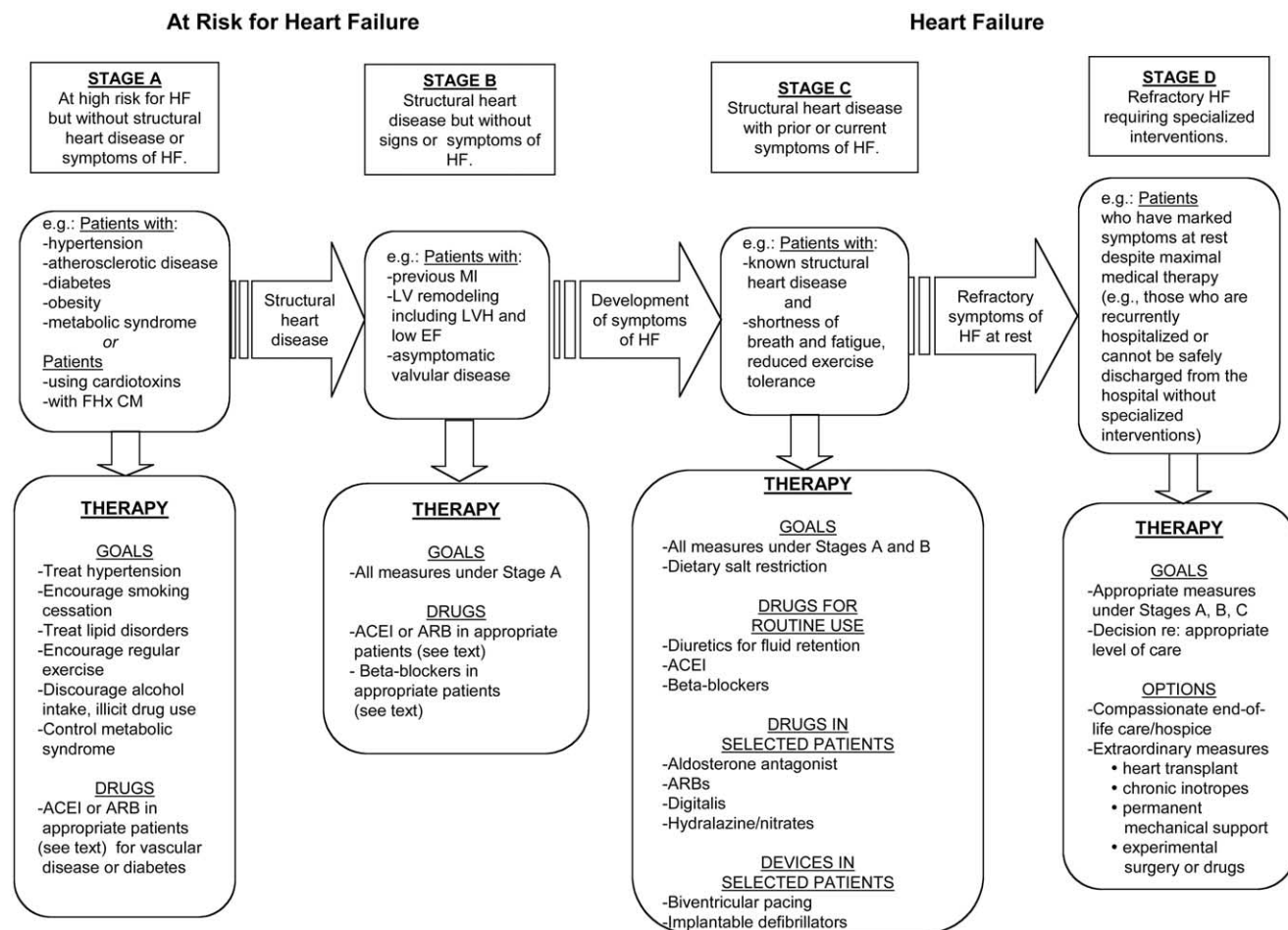


Figure 1. Stages in the development of HF/recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; ACEI, angiotensin converting enzyme inhibitors; and ARB, angiotensin receptor blocker.

- Twelve-lead electrocardiogram and chest radiograph (**PA and lateral**) should be performed initially in all patients presenting with HF. (Level of Evidence: C)
- Two-dimensional echocardiography with Doppler should be performed during initial evaluation of patients presenting with HF to assess LVEF, **LV size, wall thickness, and valve function**. Radionuclide ventriculography can be performed to assess LVEF and volumes. (Level of Evidence: C)
- Coronary arteriography should be performed in patients presenting with HF who have angina or **significant ischemia unless the patient is not eligible for revascularization of any kind**. (Level of Evidence: B)

CLASS IIA

- Coronary arteriography is reasonable for patients presenting with HF who have chest pain **that may or may not be of cardiac origin** who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization. (Level of Evidence: C)
- Coronary arteriography is reasonable for patients presenting with HF who have known or suspected coronary artery disease but who do not have angina **unless the patient is not eligible for revascularization of any kind**. (Level of Evidence: C)

- Noninvasive imaging to detect **myocardial** ischemia and viability is reasonable in patients presenting with HF who have known coronary artery disease and no angina **unless the patient is not eligible for revascularization of any kind**. (Level of Evidence: B)
- Maximal exercise testing with **or without** measurement of respiratory gas exchange and/or blood oxygen saturation is reasonable in patients presenting with HF to help determine whether HF is the cause of exercise limitation when the contribution of HF is uncertain. (Level of Evidence: C)
- Maximal exercise testing with measurement of respiratory gas exchange is reasonable to identify high-risk patients presenting with HF who are candidates for cardiac transplantation or other advanced treatments. (Level of Evidence: B)
- Screening for hemochromatosis, **sleep-disturbed breathing, or human immunodeficiency virus** is reasonable in **selected** patients who present with HF. (Level of Evidence: C)
- Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma** are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases. (Level of Evidence: C)
- Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is

suspected that would influence therapy. (*Level of Evidence: C*)

9. Measurement of B-type natriuretic peptide (BNP)* can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. (*Level of Evidence: A*)

CLASS IIB

1. Noninvasive imaging may be considered to define the likelihood of coronary artery disease in patients with HF and LV dysfunction. (*Level of Evidence: C*)
2. Holter monitoring might be considered in patients presenting with HF who have a history of MI and are being considered for electrophysiologic study to document VT inducibility. (*Level of Evidence: C*)

CLASS III

1. Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF. (*Level of Evidence: C*)
2. Routine use of signal-averaged electrocardiography is not recommended for the evaluation of patients presenting with HF. (*Level of Evidence: C*)
3. Routine measurement of circulating levels of neurohormones (e.g., norepinephrine or endothelin) is not recommended for patients presenting with HF. (*Level of Evidence: C*)

RECOMMENDATIONS FOR SERIAL CLINICAL ASSESSMENT OF PATIENTS PRESENTING WITH HF

CLASS I

1. Assessment should be made at each visit of the ability of a patient with HF to perform routine and desired activities of daily living. (*Level of Evidence: C*)
2. Assessment should be made at each visit of the volume status and weight of a patient with HF. (*Level of Evidence: C*)
3. Careful history of current use of alcohol, tobacco, illicit drugs, "alternative therapies," and chemotherapy drugs, as well as diet and sodium intake, should be obtained at each visit of a patient with HF. (*Level of Evidence: C*)

CLASS IIA

1. Repeat measurement of EF and the severity of structural remodeling can provide useful information in patients with HF who have had a change in clinical status or who have experienced or recovered from a clinical event or received treatment that might have had a significant effect on cardiac function. (*Level of Evidence: C*)

CLASS IIB

1. The value of serial measurements of BNP to guide therapy for patients with HF is not well established. (*Level of Evidence: C*)

*Note in proof: The writing committee intended BNP to indicate B-type natriuretic peptide rather than a specific type of assay. Assessment can be made using assays for BNP or N-terminal proBNP. The two types of assays yield clinically similar information.

A. Initial Evaluation of Patients

1. Identification of a Structural and Functional Abnormality

The single most useful diagnostic test in the evaluation of patients with HF is the comprehensive 2-dimensional echocardiogram coupled with Doppler flow studies to determine whether abnormalities of myocardium, heart valves, or pericardium are present and which chambers are involved. A comprehensive echocardiographic evaluation is important, because it is common for patients to have more than 1 cardiac abnormality that contributes to the development of HF. Furthermore, the study may serve as a baseline for comparison, because measurement of EF and the severity of structural remodeling can provide useful information in patients who have had a change in clinical status or who have experienced or recovered from a clinical event or received treatment that might have had a significant effect on cardiac function. Other tests such as radionuclide ventriculography or magnetic resonance imaging may also be used to provide information regarding the nature and severity of the cardiac abnormality.

2. Evaluation of the Cause of HF

a. History and Physical Examination

Evaluation of potential causative factors begins with a thorough history and careful physical examination (Table 1).

b. Laboratory Testing

Laboratory testing may reveal the presence of disorders or conditions that can lead to or exacerbate HF. The initial evaluation of patients with HF should include a complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), glycohemoglobin, and blood lipids, as well as tests of both renal and hepatic function, a chest radiograph, and a 12-lead electrocardiogram. Thyroid-function tests (especially thyroid-stimulating hormone) should be measured, because both hyperthyroidism and hypothyroidism can be a primary or contributory cause of HF.

Several recent assays have been developed for BNP and related peptides. Several of the natriuretic peptides are synthesized by and released from the heart. Elevated plasma BNP levels have been associated with reduced LVEF (13), LVH, elevated LV filling pressures, and acute MI and ischemia, although they can occur in other settings, such as pulmonary embolism and chronic obstructive pulmonary disease. They are sensitive to other biological factors, such as age, sex, weight, and renal function (14). Elevated levels lend support to a diagnosis of abnormal ventricular function or hemodynamics causing symptomatic HF (15). Trials with this diagnostic marker suggest utility in the urgent-care setting, where it has been used in combination with clinical evaluation to differentiate dyspnea due to HF from dyspnea of other causes (13,16), and suggest that its use may reduce the time to hospital discharge and the cost of treatment (17). B-type natriuretic peptide levels tend to be less elevated in HF with preserved EF than in HF with low EF and are lower in obese patients (18,19). Levels of BNP may be meaningfully elevated in women and in people over 60 years of age who do not have HF, and thus BNP levels should be interpreted

TABLE 1. Evaluation of the Cause of Heart Failure: The History

History to include inquiry regarding:

Hypertension
Diabetes
Dyslipidemia
Valvular heart disease
Coronary or peripheral vascular disease
Myopathy
Rheumatic fever
Mediastinal irradiation
History or symptoms of sleep-disordered breathing
Exposure to cardiotoxic agents
Current and past alcohol consumption
Smoking
Collagen vascular disease
Exposure to sexually transmitted diseases
Thyroid disorder
Pheochromocytoma
Obesity

Family history to include inquiry regarding:

Predisposition to atherosclerotic disease (Hx of MIs, strokes, PAD)
Sudden cardiac death
Myopathy
Conduction system disease (need for pacemaker)
Tachyarrhythmias
Cardiomyopathy (unexplained HF)
Skeletal myopathies

HF indicates heart failure; Hx, history; MI, myocardial infarction; and PAD, peripheral arterial disease.

cautiously in such individuals when distinguishing between cardiac and noncardiac causes of dyspnea (13). Elevated BNP levels may lend weight to a suspected diagnosis of HF or trigger consideration of HF when the diagnosis is unknown but should not be used in isolation to confirm or exclude the presence of HF (17,20).

B. Ongoing Evaluation of Patients

1. Assessment of Volume Status

It is critically important for healthcare providers to evaluate the fluid or volume status of patients with HF during the initial visit and each follow-up examination. This assessment plays a pivotal role in determining the need for diuretic therapy and in detecting sodium excesses or deficiencies that may limit efficacy and decrease the tolerability of drugs used to treat HF. The physical examination is the primary step in evaluating the presence and severity of fluid retention in patients with HF. At each visit, healthcare providers should record the patient's body weight and sitting and standing blood pressures and determine the degree of jugular venous distension and its response to abdominal pressure, the presence and severity of organ congestion (pulmonary rales and hepatomegaly), and the magnitude of peripheral edema in the legs, abdomen, presacral area, and scrotum, as well as ascites in the abdomen.

2. Laboratory Assessment

Serum electrolytes and renal function should be monitored routinely in patients with HF. Of particular importance is the serial measurement of serum potassium concentration, because hypokalemia is a common adverse effect of treatment with diuretics and may cause fatal arrhythmias and increase the risk of digitalis toxicity, whereas hyperkalemia may complicate therapy with angiotensin converting enzyme (ACE) inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists. Worsening renal function may require adjustment of the doses of diuretics, renin-angiotensin-aldosterone system antagonists, digoxin, and noncardiac medications. Development of hyponatremia or anemia may be a sign of disease progression and is associated with impaired survival.

Serum BNP levels have been shown to parallel the clinical severity of HF as assessed by NYHA class in broad populations. Levels are higher in hospitalized patients and tend to decrease during aggressive therapy for decompensation (see Section 3.1.3.2 on BNP in the full-text guidelines) (15). However, it cannot be assumed that BNP levels can be used effectively as targets for adjustment of therapy in individual patients. Ongoing trials will help to determine the role of serial BNP measurements in both diagnosis and management of HF.

Repeat assessment of EF may be most useful when the patient has demonstrated a major change in clinical status. Both improvement and deterioration may have important implications for future care, although the recommended medical regimen should be continued in most cases. Improvement may reflect recovery from a previous condition, such as viral myocarditis or hypothyroidism, or may occur after titration of recommended therapies for chronic HF. Deterioration may reflect gradual disease progression or a new event, such as recurrent MI. Routine assessment of EF at frequent, regular, or arbitrary intervals is not recommended.

3. Assessment of Prognosis

Although both healthcare providers and patients may be interested in defining the prognosis of an individual patient with HF, the likelihood of survival can be determined reliably only in populations and not in individuals. However, some attempt at prognostication in HF may provide better information for patients and their families to appropriately plan for their futures. It also identifies patients in whom cardiac transplantation or mechanical device therapy should be considered.

IV. Therapy

Table 2 describes cardiovascular medications useful for treatment of various stages of HF (see the Figure for an explanation of the stages of HF).

A. Patients at High Risk for Developing HF (Stage A)

RECOMMENDATIONS

CLASS I

1. In patients at high risk for developing HF, systolic and diastolic hypertension should be controlled in accordance with contemporary guidelines. (*Level of Evidence: A*)
2. In patients at high risk for developing HF, lipid disorders should be treated in accordance with contemporary guidelines. (*Level of Evidence: A*)

TABLE 2. Cardiovascular Medications Useful for Treatment of Various Stages* of Heart Failure

Drug	Stage A	Stage B	Stage C
ACE inhibitors			
Benazepril	H
Captopril	H, DN	Post MI	HF
Enalapril	H, DN	Asymptomatic LVSD	HF
Fosinopril	H	...	HF
Lisinopril	H, DN	Post MI	HF
Moexipril	H
Perindopril	H, CV Risk
Quinapril	H	...	HF
Ramipril	H, CV Risk	Post MI	Post MI
Trandolapril	H	Post MI	Post MI
Angiotensin receptor blockers			
Candesartan	H	...	HF
Eprosartan	H
Irbesartan	H, DN
Losartan	H, DN	CV Risk	...
Olmesartan	H
Telmisartan	H
Valsartan	H, DN	Post MI	Post MI, HF
Adosterone blockers			
Eplerenone	H	Post MI	Post MI
Spironolactone	H	...	HF
Beta-blockers			
Acebutolol	H
Atenolol	H	Post MI	...
Betaxolol	H
Bisoprolol	H	...	HF
Carteolol	H
Carvedilol	H	Post MI	HF, Post MI
Labetalol	H
Metoprolol succinate	H	...	HF
Metoprolol tartrate	H	Post MI	...
Nadolol	H
Penbutolol	H
Pindolol	H
Propranolol	H	Post MI	...
Timolol	H	Post MI	...
Digoxin	HF

*See Figure for explanation of stages of heart failure.

Asymptomatic LVSD indicates Asymptomatic left ventricular systolic dysfunction; CV Risk, reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure and asymptomatic left ventricular dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

- For patients with diabetes mellitus (who are all at high risk for developing HF), blood sugar should be controlled in accordance with contemporary guidelines. (Level of Evidence: C)
- Patients at high risk for developing HF should be counseled to avoid behaviors that may increase the risk of HF

(e.g., smoking, excessive alcohol consumption, and illicit drug use). (Level of Evidence: C)

- Ventricular rate should be controlled or sinus rhythm restored in patients with supraventricular tachyarrhythmias who are at high risk for developing HF. (Level of Evidence: B)
- Thyroid disorders should be treated in accordance with contemporary guidelines in patients at high risk for developing HF. (Level of Evidence: C)
- Healthcare providers should perform periodic evaluation for signs and symptoms of HF in patients at high risk for developing HF. (Level of Evidence: C)
- In patients at high risk for developing HF who have known atherosclerotic vascular disease, healthcare providers should follow current guidelines for secondary prevention. (Level of Evidence: C)
- Healthcare providers should perform a noninvasive evaluation of LV function (i.e., LVEF) in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions. (Level of Evidence: C)

CLASS IIA

- Angiotensin converting enzyme inhibitors can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (Level of Evidence: A)
- Angiotensin II receptor blockers can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (Level of Evidence: C)

CLASS III

- Routine use of nutritional supplements solely to prevent the development of structural heart disease should not be recommended for patients at high risk for developing HF. (Level of Evidence: C)

1. Control of Risk

a. Treatment of Hypertension

Elevated levels of diastolic and especially systolic blood pressure are major risk factors for the development of HF (21,22), and long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of HF (23-25). A number of large, controlled studies have quite uniformly demonstrated that optimal blood pressure control decreases the risk of new HF by approximately 50% (26).

Healthcare providers should lower both systolic and diastolic blood pressure in accordance with the recommendations provided in published guidelines, including the most recently published report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (27); target levels of blood pressure are lower in patients with associated major cardiovascular risk factors, especially those with diabetes mellitus (27a,27b). When an antihypertensive regimen is devised, optimal control of blood pressure should remain as the primary goal, with the choice of drugs determined by the concomitant medical problems (e.g., coronary artery disease, diabetes, or renal disease). Diuretic-based antihypertensive therapy has repeatedly been shown to

prevent HF in a wide range of target populations (30). Angiotensin converting enzyme inhibitors and beta-blockers are also effective in the prevention of HF (27), whereas calcium antagonists and alpha-blockers are less effective in preventing HF syndrome (31). However, ACEIs and beta-blockers, as single therapies, are not superior to other antihypertensive drug classes in the reduction of all cardiovascular outcomes. Nevertheless, among patients with diabetes or other cardiovascular complications (32,33), ACEIs have been most notable with respect to a reduction in the onset of HF and new-onset diabetes. Likewise, compared with placebo, the ARBs losartan (34) and irbesartan (35) significantly reduced the incidence of HF in patients with type 2 diabetes mellitus and nephropathy. Ultimately, an appropriate antihypertensive regimen frequently consists of several drugs used in combination. Although prevention of HF is the focus of these guidelines, overall cardiovascular preventative strategies have also been the subject of published guidelines (36).

b. Treatment of Diabetes

Obesity and insulin resistance are important risk factors for the development of HF (28,37). The presence of clinical diabetes mellitus markedly increases the likelihood of HF in patients without structural heart disease (29) and adversely affects the outcomes of patients with established HF (38,39). In a study of patients with type 2 diabetes mellitus more than 50 years of age who had urinary albumin greater than 20 mg per liter, 4% of patients developed HF over the study period, of whom 36% died (40). The occurrence of HF represents a major and adverse prognostic turn in a diabetic patient's life. There is a differential gender effect associated with this risk; diabetes mellitus only modestly increases the risk of HF for men, but it increases the relative risk of HF more than 3-fold among women (21). Healthcare providers should make every effort to control hyperglycemia, although such control has not yet been shown to reduce the subsequent risk of HF. In addition, ACEIs or ARBs can prevent the development of end-organ disease and the occurrence of clinical events in diabetic patients, even in those who do not have hypertension (32,41). Long-term treatment with several ACEIs or ARBs has been shown to decrease the risk of renal disease in diabetic patients (42,42a), and prolonged therapy with the ACEI ramipril has been shown to lower the likelihood of cardiovascular death, MI, and HF (32). Likewise, the use of ARBs in patients with diabetes mellitus and hypertension or LVH has been shown to reduce the incidence of first hospitalization for HF, in addition to having other beneficial effects on renal function (34,35,43).

c. Management of the Metabolic Syndrome

The clustering of cardiovascular risk factors in individual patients, termed the metabolic syndrome or syndrome X, includes any 3 of the criteria of abdominal adiposity, hypertriglyceridemia, low high-density lipoprotein, hypertension, and fasting hyperglycemia. It is estimated that the prevalence of the metabolic syndrome in the United States exceeds 20% of individuals who are at least 20 years of age, and 40% of the population over 40 years of age (44). A number of trials are currently in progress to determine the most effective intervention for patients with the metabolic syndrome.

d. Management of Atherosclerotic Disease

Patients with known atherosclerotic disease (e.g., of the coronary, cerebral, or peripheral blood vessels) are likely to develop HF, and healthcare providers should seek to control vascular risk factors in such patients according to recommended guidelines (36). In one large-scale trial, long-term treatment with an ACEI decreased the risk of the primary end point of cardiovascular death, MI, and stroke in patients with established vascular disease who were without evidence of HF or reduced LVEF at the time of randomization, but the incidence of new HF was not a primary or secondary end point although it was improved (32). Among patients with established coronary artery disease and no HF, another ACEI significantly reduced the incidence of death, MI or cardiac arrest (33). A more recent large trial of ACEI versus placebo failed to show a reduction in the primary composite end point, although a post hoc analysis did show some reduction in HF hospitalization (44a). The committee, in reviewing the accruing data, decided to change the level of recommendation for the use of ACEI for Stage A patients from Class I in the 2001 document to Class IIa in this document. Treatment of hyperlipidemia (in accordance with published guidelines) has been shown to reduce the likelihood of death and of HF in patients with a history of MI (45,45a,45b,45c).

e. Control of Conditions That May Cause Cardiac Injury

Many therapeutic and recreational agents can exert important cardiotoxic effects, and patients should be strongly advised about the hazards of smoking, as well as the use of alcohol, cocaine, amphetamines, and other illicit drugs. Several epidemiological studies have revealed no correlation between the amount of alcohol ingested and the subsequent development of HF; nevertheless, the Writing Committee strongly believed that any patient with a history of alcohol abuse or with current substantial routine alcohol consumption and new-onset HF without other obvious cause should be counseled to become abstinent. Many HF programs limit alcoholic beverage consumption to no more than 1 alcoholic beverage serving daily for all patients with LV dysfunction, regardless of cause (46,47). Use of ephedra, formerly a common ingredient in over-the-counter weight loss preparations, may contribute to the development of HF as well (48).

f. Other Measures

There is no direct evidence that control of dietary sodium or participation in regular exercise can prevent the development of HF. However, in patients with hypertension or other vascular disease, these efforts may have other health benefits and may enhance a general sense of well-being.

2. Early Detection of Structural Abnormalities

Asymptomatic patients with ventricular dilatation and reduced LVEF carry substantially higher risk for subsequent morbidity and mortality than the general population. It would be desirable to construct cost-effective strategies to identify such patients in the interest of reducing their subsequent risk. Limited information is available to support the cost-effectiveness of broad population screening. Brain natriuretic peptide levels represent a potential tool for this purpose (49). An analysis of the implications of elevated BNP has suggested that the screening of asymp-

tomatic people over the age of 60 years with this blood test could yield cost-effective improvement in clinical outcomes across the population (50).

B. Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed HF Symptoms (Stage B)

RECOMMENDATIONS

CLASS I

1. All Class I recommendations for Stage A should apply to patients with cardiac structural abnormalities who have not developed HF. (*Levels of Evidence: A, B, and C as appropriate*)
2. **Beta-blockers and ACEIs** should be used in **all** patients with a recent or remote history of MI regardless of EF or presence of HF (see Table 2). (*Level of Evidence: A*)
3. Beta-blockers are indicated in **all** patients without a history of MI who have a reduced LVEF with no HF symptoms (see Table 2 and text). (*Level of Evidence: C*)
4. Angiotensin converting enzyme inhibitors should be used in patients with a reduced EF and no symptoms of HF, even if they have not experienced MI. (*Level of Evidence: A*)
5. An ARB should be administered to post-MI patients without HF who are intolerant of ACE inhibitors and have a low LVEF. (*Level of Evidence: B*)
6. Patients who have not developed HF symptoms should be treated according to contemporary guidelines after an acute MI. (*Level of Evidence: C*)
7. Coronary revascularization should be recommended in appropriate patients without symptoms of HF in accordance with contemporary guidelines (see ACC/AHA Guidelines for the Management of Patients With Chronic Stable Angina). (*Level of Evidence: A*)
8. Valve replacement or repair should be recommended for patients with hemodynamically significant valvular stenosis or regurgitation and no symptoms of HF in accordance with contemporary guidelines. (*Level of Evidence: B*)

CLASS IIA

1. Angiotensin converting enzyme inhibitors or ARBs can be beneficial in patients with hypertension and LVH and no symptoms of HF. (*Level of Evidence B*)
2. Angiotensin II receptor blockers can be beneficial in patients with low EF and no symptoms of HF who are intolerant of ACEIs. (*Level of Evidence: C*)
3. Placement of an ICD is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are NYHA functional class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (*Level of Evidence: B*)

CLASS IIB

1. Placement of an implantable cardioverter-defibrillator might be considered in patients without HF who have nonischemic cardiomyopathy and an LVEF less than or equal to 30% who are in NYHA functional Class I with chronic optimal medical therapy and have a reasonable expectation of sur-

vival with good functional status for more than 1 year. (*Level of Evidence: C*)

CLASS III

1. Digoxin should not be used in patients with **low EF**, sinus rhythm, and **no history of HF symptoms, because in this population, the risk of harm is not balanced by any known benefit.** (*Level of Evidence: C*)
2. Use of nutritional supplements to treat structural heart disease or to prevent the development of symptoms of HF is not recommended. (*Level of Evidence: C*)
3. **Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI (see text in Stage C).** (*Level of Evidence: C*)

1. Prevention of Cardiovascular Events

a. Patients With an Acute MI

For recommendations on the treatment of patients with MI, see the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (9).

b. Patients With Chronic Reduction of LVEF but No Symptoms

Long-term treatment with an ACEI has been shown to delay the onset of HF symptoms and decrease the combined risk of death and hospitalization for HF in asymptomatic patients with reduced LVEF, whether due to a remote ischemic injury or to a nonischemic cardiomyopathy (51,52). Although a recent trial investigated patients with low EF and HF at the time of MI, there are no studies that specifically address use of ARBs in asymptomatic patients with reduced LVEF. Given the results of studies in symptomatic patients with low EF, ARBs may be an appropriate alternative, particularly in patients who cannot tolerate an ACEI. Furthermore, although controlled clinical trials are lacking, the use of beta-blockers in patients with a low EF and no symptoms (especially those with coronary artery disease) is also recommended (53,54). In such cases, the same beta-blockers should be used that were employed in the large HF trials.

The use of ICD therapy in patients with chronic reduction of LVEF but no symptoms has been evaluated in one large trial including only patients with ischemic cardiomyopathy. The trials assessing ICD for primary prophylaxis in nonischemic cardiomyopathy have not included functional class I patients, and the efficacy of ICDs in this population as a whole is unknown (54a). The trial involving patients with ischemic cardiomyopathy included a subset of asymptomatic patients post-MI with LVEF 30% or less, and there was demonstrated benefit of ICD placement (MADIT-II) in that subset. The findings potentially apply to large numbers of patients, and the number needed to treat to have benefit would be great. The writing committee struggled with this issue because guidelines are meant to summarize current science and not take into account economic issues or the societal impact of making a recommendation. However, the committee recognizes that economic impact and societal issues will clearly modulate how these recommendations are implemented.

TABLE 3. Oral Diuretics Recommended for Use in the Treatment of Fluid Retention in Chronic Heart Failure

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
Potassium-sparing diuretics			
Amiloride	5 mg once	20 mg	24 hours
Spironolactone	12.5 to 25 mg once	50 mg*	2 to 3 days
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
Sequential nephron blockade			
Metolazone	2.5 to 10 mg once plus loop diuretic		
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic		
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic		

mg indicates milligrams.

*Higher doses may occasionally be used with close monitoring.

In contrast, there are no data to recommend the use of digoxin in patients with asymptomatic reduction of LVEF, except in those with atrial fibrillation. Likewise, there are no data to recommend the routine use of calcium channel blockers in patients with asymptomatic reduction of LVEF, but they have not been shown to have adverse effects and may be helpful for concomitant conditions such as hypertension. However, the use of calcium channel blockers with negative inotropic effects is not recommended in asymptomatic patients with EF less than 40% after MI (55).

C. Patients With Current or Prior Symptoms of HF (Stage C)

1. Patients With Reduced LVEF

RECOMMENDATIONS

CLASS I

- Measures listed as Class I recommendations for patients in stages A and B are also appropriate for patients in Stage C. (Levels of Evidence: A, B, and C as appropriate)
- Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention (see Table 3). (Level of Evidence: C)
- Angiotensin converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 2 and text). (Level of Evidence: A)
- Beta-blockers (using 1 of the 3 proven to reduce mortality, ie, bisoprolol, carvedilol, and sustained

release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 2 and text). (Level of Evidence: A)

- Angiotensin II receptor blockers approved for the treatment of HF (see Table 2) are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI intolerant (see text for information regarding patients with angioedema). (Level of Evidence: A)
- Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text). (Level of Evidence: B)
- Exercise training is beneficial as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: B)
- An implantable cardioverter-defibrillator is recommended as secondary prevention to prolong survival in patients with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. (Level of Evidence: A)
- Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with ischemic heart disease who are at least 40 days post-MI, have an LVEF less than or equal to 30%, with NYHA functional class

II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (*Level of Evidence: A*)

10. Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with nonischemic cardiomyopathy who have an LVEF less than or equal to 30%, with NYHA functional class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (*Level of Evidence: B*)
11. Patients with LVEF less than or equal to 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dys-synchrony, which is currently defined as a QRS duration greater than 0.12 ms, should receive cardiac resynchronization therapy unless contraindicated. (*Level of Evidence: A*)
12. Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. (Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.) (*Level of Evidence: B*)

CLASS IIA

1. Angiotensin II receptor blockers are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. (*Level of Evidence: A*)
2. Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. (*Level of Evidence: B*)
3. The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms. (*Level of Evidence: A*)
4. Placement of an implantable cardioverter-defibrillator is reasonable in patients with LVEF of 30% to 35% of any origin with NYHA functional class II or III symptoms who are taking chronic optimal medical therapy and who have reasonable expectation of survival with good functional status of more than 1 year. (*Level of Evidence: B*)

CLASS IIB

1. A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency. (*Level of Evidence: C*)

2. The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. (*Level of Evidence: B*)

CLASS III

1. Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF. (*Level of Evidence: C*)
2. Calcium channel blocking drugs are not indicated as routine treatment for HF in patients with current or prior symptoms of HF and reduced LVEF. (*Level of Evidence: A*)
3. Long-term use of an infusion of a positive inotropic drug may be harmful and is not recommended for patients with current or prior symptoms of HF and reduced LVEF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for Stage D). (*Level of Evidence: C*)
4. Use of nutritional supplements as treatment for HF is not indicated in patients with current or prior symptoms of HF and reduced LVEF. (*Level of Evidence: C*)
5. Hormonal therapies other than to replete deficiencies are not recommended and may be harmful to patients with current or prior symptoms of HF and reduced LVEF. (*Level of Evidence: C*)

a. General Measures

Additions were made to the 3 classes of drugs that can exacerbate the syndrome of HF and that should be avoided in most patients:

1. Antiarrhythmic agents: Only amiodarone and dofetilide have been shown not to adversely affect survival (56).
2. Calcium channel blockers: Only the vasoselective ones have been shown not to adversely affect survival (57,58).
3. Nonsteroidal anti-inflammatory drugs: A discussion of the use of aspirin as a unique agent is found later in this section.

Patients with HF should be monitored carefully for changes in serum potassium, and every effort should be made to prevent the occurrence of either hypokalemia or hyperkalemia. Many experts believe that serum potassium concentrations should be targeted in the 4.0 to 5.0 mmol per liter range.

b. Drugs Recommended for Routine Use

DIURETICS

Thiazide diuretics may be preferred in hypertensive HF patients with mild fluid retention because they confer more persistent antihypertensive effects. Tables 3 and 4 illustrate oral and intravenous diuretics recommended for use in the treatment of chronic HF.

INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Inhibition of the renin-angiotensin-aldosterone system can take place at multiple sites: at the level of the enzyme that converts angiotensin I to angiotensin II (ACEIs), at the angiotensin receptor (ARBs), or at the receptor for aldosterone, which is under control of both the renin-angiotensin

TABLE 4. Intravenous Diuretic Medications Useful for the Treatment of Severe Heart Failure

Drug	Initial Dose	Maximum Single Dose
Loop diuretics		
Bumetanide	1.0 mg	4 to 8 mg
Furosemide	40 mg	160 to 200 mg
Torsemide	10 mg	100 to 200 mg
Thiazide diuretics		
Chlorothiazide	500 mg	1000 mg
Sequential nephron blockade Chlorothiazide 500 to 1000 mg (IV) once or twice plus loop diuretics once—multiple doses per day Metozalone (as Zaroxolyn or Diulo) 2.5 to 5 mg (p.o.) once or twice daily with loop diuretic		
IV infusions		
Bumetanide	1-mg IV load then 0.5- to 2-mg-per-hour infusion	
Furosemide	40-mg IV load then 10- to 40-mg-per-hour infusion	
Torsemide	20-mg IV load then 5- to 20-mg -per-hour infusion	

IV indicates intravenous; mg, milligrams.

system and other systemic and local influences (aldosterone antagonists). ACEIs are the best studied class of agents in HF, with multiple mechanisms of benefit for both HF, coronary disease, and other atherosclerotic vascular disease, as well as diabetic nephropathy. During chronic therapy with ACEIs, the renin-angiotensin system demonstrates partial “escape” from inhibition with “normalization” of angiotensin levels, in part owing to alternative local pathways for production of angiotensin. This leaves the potential for benefit from additional therapy with ARBs and with the aldosterone antagonists.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Analysis of a large collective experience indicates that ACEIs can alleviate symptoms, improve clinical status, and enhance the overall sense of well-being of patients with HF (59–70). In addition, ACEIs can reduce the risk of death and the combined risk of death or hospitalization (59,60,70). These benefits of ACE inhibition were seen in patients with mild, moderate, or severe symptoms and in patients with or without coronary artery disease.

PRACTICAL USE OF ACE INHIBITORS: SELECTION OF PATIENTS

Angiotensin converting enzyme inhibitors should be prescribed to all patients with HF due to LV systolic dysfunction with reduced LVEF unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs. Because of their favorable effects on survival, treatment with an ACEI should not be delayed until the patient is found to be resistant to treatment with other drugs. ACEIs are often preferred over the use of ARBs or direct-acting vasodilators (70,71) because of the greater experience and weight of evidence supporting their effectiveness.

Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACEI cannot be used or are poorly tolerated, intermediate doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses. More importantly, clinicians should not delay the institution of beta-blockers in patients because of a failure to reach target ACEI doses.

Two retrospective reviews have reported no adverse effects of concomitant aspirin use with ACEIs on long-term survival (72,73). Given these retrospective results, many physicians believe the data justify prescribing aspirin and ACEIs together when there is an indication for use of aspirin. These large overviews are subject to varying interpretation. Other physicians would consider not combining aspirin with an ACEI because there are no data to indicate that it can reduce the risk of ischemic events in patients with HF (74,75), or they might consider the use of an alternative antiplatelet agent such as clopidogrel, which does not interact with ACEIs and which may have superior effects in preventing ischemic events (76). However, clopidogrel does not have an indication for the primary prevention of ischemic events. There may be an important interaction between aspirin and ACEIs, but there is controversy regarding this point, and it requires further study.

Although ARBs may be considered as alternative therapy for patients who have developed angioedema while taking an ACEI, there are a small number of patients who have also developed angioedema with ARBs and extreme caution is advised when substituting an ARB in a patient who has had angioedema associated with ACEI use (77–79,79a).

ANGIOTENSIN II RECEPTOR BLOCKERS

Table 5 lists the inhibitors of the renin-angiotensin-aldosterone system and beta-blockers that are commonly used for the treatment of patients with HF with low EF.

Experience with ARBs in controlled clinical trials of patients with HF is considerably less than that with ACEIs. Nevertheless, in several placebo-controlled studies, long-term therapy with ARBs produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system (80–86).

For patients unable to tolerate ACEIs because of cough or angioedema, the ARBs valsartan and candesartan (79,87) have demonstrated benefit by reducing hospitalizations and mortality. The combination of an ACEI and ARBs may produce more reduction of LV size than either agent alone (88). The addition of ARBs to chronic ACEI therapy caused

TABLE 5. Inhibitors of the Renin-Angiotensin-Aldosterone System and Beta-Blockers Commonly Used for the Treatment of Patients With HF With Low Ejection Fraction

Drug	Initial Daily Dose(s)	Maximum Dose(s)
ACE inhibitors		
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 to 20 mg twice
Fosinopril	5 to 10 mg once	40 mg once
Lisinopril	2.5 to 5 mg once	20 to 40 mg once
Perindopril	2 mg once	8 to 16 mg once
Quinapril	5 mg twice	20 mg twice
Ramipril	1.25 to 2.5 mg once	10 mg once
Trandolapril	1 mg once	4 mg once
Angiotensin receptor blockers		
Candesartan	4 to 8 mg once	32 mg once
Losartan	25 to 50 mg once	50 to 100 mg once
Valsartan	20 to 40 mg twice	160 mg twice
Aldosterone antagonists		
Spironolactone	12.5 to 25 mg once	25 mg once or twice
Eplerenone	25 mg once	50 mg once
Beta-blockers		
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	25 mg twice (50 mg twice for patients >85 kg)
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once

ACE indicates angiotensin-converting enzyme; kg, kilograms; and mg, milligrams.

a modest decrease in hospitalization in 2 studies, with a trend to decreased total mortality in one and no impact on mortality in another (87–89).

PRACTICAL USE OF ARBs

When used, angiotensin receptor antagonists should be initiated with the starting doses shown in Table 5. Many of the considerations with ARB are similar to those with initiation of an ACEI, as discussed above. Blood pressure (including postural blood pressure changes), renal function, and potassium should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in doses. Patients with systolic blood pressure below 80 mm Hg, low serum sodium, diabetes mellitus, and impaired renal function merit particular surveillance during therapy with inhibitors of the renin-angiotensin-aldosterone system. Titration is generally achieved by doubling doses. For stable patients, it is reasonable to add therapy with beta-blocking agents before full target doses of either ACEIs or ARBs are reached.

The risks of treatment with ARBs are those attributed to suppression of angiotensin stimulation, as discussed above for ACEIs. These risks of hypotension, renal dysfunction, and hyperkalemia are greater when combined with another inhibitor of this axis, such as ACEIs or aldosterone antagonists.

ALDOSTERONE ANTAGONISTS

In a large-scale, long-term trial (90), low doses of spironolactone (starting at 12.5 mg daily) were added to ACEI therapy for patients with class IV HF symptoms or class III symptoms and recent hospitalization. The risk of death was

reduced from 46% to 35% (30% relative risk reduction) over 2 years, with 35% reduction in HF hospitalization and an improvement in functional class. Initial creatinine levels were below 2.0 mg per dl in the dose-ranging pilot trial and below 2.5 mg per dl in the main trial. Potassium replacements were stopped at trial entry, and serum potassium and renal function were followed very closely.

A recent trial investigated the newer aldosterone antagonist eplerenone in patients with LVEF less than or equal to 40% and clinical evidence of HF or diabetes mellitus within 14 days of MI. Mortality was decreased from 13.6% to 11.8% at 1 year. Hyperkalemia occurred in 5.5% of patients treated with eplerenone compared with 3.9% of those given placebo overall and in up to 10.1% versus 4.6% of patients with estimated creatinine clearance less than 50 ml per min (94).

RECOMMENDATIONS CONCERNING ALDOSTERONE ANTAGONISTS

The addition of low-dose aldosterone antagonists should be considered in carefully selected patients with moderately severe or severe HF symptoms and recent decompensation or with LV dysfunction early after MI. These recommendations are based on the strong data demonstrating reduced death and rehospitalization in 2 clinical trial populations (90,94). To minimize the risk of life-threatening hyperkalemia in patients with low LVEF and symptoms of HF, patients should have initial serum creatinine less than 2.0 mg per dl to 2.5 mg per dl without recent worsening and serum potassium less than 5.0 mEq per dl without a history of severe hyperkalemia. The safety of the combination of ACEIs, ARBs, and aldosterone

TABLE 6. Guidelines for Minimizing the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine exceeds 1.6 mg per dl.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance exceeds 30 ml per min is recommended.
2. Aldosterone antagonists should not be administered to patients with baseline serum potassium in excess of 5.0 mEq per liter.
3. An initial dose of spironolactone 12.5 mg or eplerenone 25 mg is recommended, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.
4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACEIs (captopril greater than or equal to 75 mg daily; enalapril or lisinopril greater than or equal to 10 mg daily).
5. Nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors should be avoided.
6. Potassium supplements should be discontinued or reduced.
7. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months.
8. Diarrhea or other causes of dehydration should be addressed emergently.

ACEIs indicates angiotensin converting enzyme inhibitors.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine greater than 2.5 mg per dl, the majority of patients had creatinine much lower; in 1 trial⁽⁹⁴⁾, 95% of patients had creatinine less than or equal to 1.7 mg per dl.

antagonists has not been explored adequately, and this combination cannot be recommended.

PRACTICAL USE OF ALDOSTERONE ANTAGONISTS:

SELECTION OF PATIENTS

Decisions regarding the selection of patients for aldosterone antagonists reflect the balance between potential benefit to decrease death and hospitalization from HF and potential risks of life-threatening hyperkalemia. Serum creatinine levels often underestimate renal dysfunction, particularly in the elderly, in whom estimated creatinine clearance less than 50 ml per min should trigger a reduction of the initial dose of spironolactone to 12.5 mg daily or of eplerenone to 25 mg daily, and aldosterone antagonists should not be given when clearance is less than 30 ml per min (see Table 6). Patients chronically requiring high doses of diuretics without potassium replacement should be evaluated closely, because potassium handling may be impaired.

The major risk of aldosterone antagonists is hyperkalemia due to inhibition of potassium excretion. The positive results of a recent trial led to wider use of spironolactone in HF regimens. The subsequent incidence of hyperkalemia was reported to be as high as 24% in 1 series⁽⁹³⁾, in which half of the subjects with hyperkalemia had potassium levels in excess of 6 mEq per liter. Similar results were reported from Norway⁽⁹²⁾. Although this far exceeded the 2% incidence in the large trial, it is comparable to the 13% observed in the preceding pilot trial with a 25-mg dose and 20% with a 50-mg dose.

The potential impact on the overall HF population is suggested by a population-based analysis in Ontario, Canada

of over 30,000 patients on ACE inhibitors after a HF hospitalization. After publication of these trial results in 1999, prescriptions for spironolactone in this geographic area more than tripled, the rate of hospitalization for hyperkalemia increased from 2.4 to 11 patients per thousand, and the associated mortality increased from 0.3 to 2 per thousand⁽⁹³⁾.

PRACTICAL USE OF ALDOSTERONE ANTAGONISTS:

INITIATION AND MONITORING

Spironolactone should be initiated at a dose of 12.5 to 25 mg daily, or occasionally on alternate days. Eplerenone was used after MI in one study⁽⁹⁴⁾ at doses of 25 mg per d, increasing to 50 mg daily. Potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high potassium-containing foods. However, patients who have required large amounts of potassium supplementation may need to continue receiving supplementation, albeit at a lower dose, particularly when previous episodes of hypokalemia have been associated with ventricular arrhythmias. On the other hand, potassium supplementation required during vigorous therapy of fluid overload is often no longer necessary once the goal is to maintain even fluid balance. Patients should be cautioned to avoid the addition of nonsteroidal anti-inflammatory agents and cyclo-oxygenase-2 inhibitors, which can lead to worsening renal function and hyperkalemia. Potassium levels and renal function should be rechecked within 3 days and again at 1 week after initiation of an aldosterone antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 3 months and every 3 months thereafter. The addition or an increase in dosage of ACEIs or ARBs should trigger a new cycle of monitoring. In view of the potential risk for hyperkalemia, the committee recommends that the routine triple combination of ACEIs, ARBs, and an aldosterone antagonist be avoided.

The development of potassium levels in excess of 5.5 mEq per liter should generally trigger discontinuation or dose reduction of the aldosterone antagonist unless patients have been receiving potassium supplementation, which should then be stopped. The development of worsening renal function should lead to careful evaluation of the entire medical regimen and consideration for stopping the aldosterone antagonist. Patients should be instructed specifically to stop the aldosterone antagonist during an episode of diarrhea or while loop diuretic therapy is interrupted.

BETA-ADRENERGIC RECEPTOR BLOCKERS

Beta-blockers act principally to inhibit the adverse effects of the sympathetic nervous system in patients with HF, and these effects far outweigh their well-known negative inotropic effects. Three beta-blockers have been shown to be effective in reducing the risk of death in patients with chronic HF: bisoprolol⁽⁹⁵⁾ and sustained-release metoprolol (succinate)⁽⁹⁶⁾, which selectively block beta-1-receptors, and carvedilol^(101,102), which blocks alpha-1, beta-1-, and beta-2- receptors. Positive findings with these 3 agents, however, should not be considered indicative of a beta-

blocker class effect (98–100). Patients who have Stage C HF should be treated with 1 of these 3 beta-blockers. The relative efficacy among these 3 agents is not known, but available evidence does suggest that beta-blockers can differ in their effects on survival (98).

EFFECT OF BETA-BLOCKERS IN THE MANAGEMENT OF HF

Beta-blockers have now been evaluated in more than 20 000 patients with HF who participated in more than 20 published placebo-controlled clinical trials (101,102). This collective experience indicates that long-term treatment with beta-blockers can lessen the symptoms of HF, improve the clinical status of patients, and enhance the patient's overall sense of well-being (95,103–109). In addition, like ACEIs, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization (95,110–113).

PRACTICAL USE OF BETA-BLOCKERS: SELECTION OF PATIENTS

Because of its favorable effects on survival and disease progression, treatment with a beta-blocker should be initiated as soon as LV dysfunction is diagnosed. Even when symptoms are mild or have responded to other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented during treatment with other drugs. Beta-blockers may be considered in patients who have reactive airway disease or asymptomatic bradycardia but should be used with great caution or not at all in patients with persistent symptoms of either condition.

INITIATION AND MAINTENANCE

Treatment with a beta-blocker should be initiated at very low doses (see Table 5), followed by gradual increments in dose if lower doses have been well tolerated. Recent data show that beta-blockers can be safely started before discharge, even in patients hospitalized for HF, provided they do not require intravenous therapy for HF (114).

DIGITALIS

The Writing Committee has re-evaluated the evidence pertinent to the value of digitalis therapy in patients with HF. Although no new data or trials using digitalis have emerged since publication of the 2001 guidelines, the Writing Committee believes that in terms of safety and efficacy, digitalis does not compare favorably with such agents as the aldosterone blockers, to which the Writing Committee has assigned a Class IIa level of recommendation. If digitalis were a new drug with clinical trials showing a very narrow risk/benefit ratio (especially for potential use in the aging population) and no mortality benefit, it would clearly not be considered for a Class I recommendation. The Writing Committee, therefore, decided to change the level of recommendation for digitalis glycosides from Class I to Class IIa in the current document.

VENTRICULAR ARRHYTHMIAS AND PREVENTION OF SUDDEN DEATH

Sudden death can be decreased meaningfully by the therapies that decrease disease progression, as discussed elsewhere in these guidelines, and by the use of implanted devices that terminate sustained arrhythmias.

SECONDARY PREVENTION OF SUDDEN DEATH

Patients with previous cardiac arrest or documented sustained ventricular arrhythmias have a high risk of recurrent events. Implantation of an implantable cardioverter-defibrillator (ICD) has been shown to reduce mortality in cardiac arrest survivors. An ICD is indicated for secondary prevention of death due to ventricular tachyarrhythmias in patients with otherwise good clinical function and prognosis, for whom prolongation of survival is a goal. Patients with chronic HF and a low EF who experience syncope of unclear origin have a high rate of subsequent sudden death and should also be considered for placement of an ICD (115). However, when ventricular tachyarrhythmias occur in a patient with a progressive and irreversible downward spiral of clinical HF decompensation, placement of an ICD is not indicated to prevent recurrence of sudden death, because death is likely imminent regardless of mode. An exception may exist for the small minority of patients for whom definitive therapy such as cardiac transplantation is planned.

PRIMARY PREVENTION OF SUDDEN DEATH

Patients with low EF without prior history of cardiac arrest, spontaneous ventricular tachycardia (VT), or inducible VT (positive programmed electrical stimulation study) have a risk of sudden death that is lower than for those who have experienced previous events, but it remains significant. Within this group, it has not yet been possible to identify those patients at highest risk, especially in the absence of prior MI.

Amiodarone has been associated with overall neutral effects on survival when given to patients with low EF and HF (116–119). Amiodarone therapy may also act through mechanisms other than antiarrhythmic effects, because amiodarone has been shown in some trials to increase LVEF and decrease the incidence of worsening HF (117,118). Side effects of amiodarone have included thyroid abnormalities, pulmonary toxicity, hepatotoxicity, neuropathy, insomnia, and numerous other reactions. Therefore, amiodarone should not be considered as part of the routine treatment of patients with HF, with or without frequent premature ventricular depolarizations or asymptomatic nonsustained VT; however, it remains the agent most likely to be safe and effective when antiarrhythmic therapy is necessary to prevent recurrent atrial fibrillation or symptomatic ventricular arrhythmias. Other pharmacological antiarrhythmic therapies, apart from beta-blockers, are rarely indicated in HF but may occasionally be used to suppress recurrent ICD shocks when amiodarone has been ineffective or discontinued owing to toxicity.

ROLE OF ICDs IN THE PRIMARY PREVENTION OF SUDDEN DEATH

The role of ICD implantation for the primary prevention of sudden death in patients with HF and low EF and no history of spontaneous or inducible VT has been addressed by several large trials that used only readily available clinical data as entry criteria (119–121). ICDs are highly effective in preventing death due to ventricular tachyarrhythmias; however, frequent shocks from an ICD can lead to a reduced quality of life. For symptoms from recurrent discharges triggered by ventricular arrhythmias or atrial fibrillation, antiarrhythmic therapy, most often amiodarone, may be added. For recurrent ICD discharges from VT despite antiarrhythmic therapy, catheter ablation may be effective (122).

It is important to recognize that ICDs have the potential to aggravate HF and have been associated with an increase in

HF hospitalizations (120,123). This may result from right ventricular pacing that produces dyssynchronous cardiac contraction; however, the occurrence of excess nonsudden events with ICDs placed early after MI suggests that other factors may also limit the overall benefit from ICDs. Careful attention to the details of ICD implantation, programming, and pacing function is important for all patients with low EF who are treated with an ICD. The ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (124) provides further discussion of the potential problem of worsening HF and LV function in all patients with right ventricular pacing.

The decision regarding the balance of potential risks and benefits of ICD implantation for an individual patient thus remains a complex one. A decrease in incidence of sudden death does not necessarily translate into decreased total mortality, and decreased total mortality does not guarantee a prolongation of survival with meaningful quality of life. This concept is particularly important in patients with limited prognosis owing to advanced HF or other serious comorbidities, because there was no survival benefit observed from ICD implantation until after the first year in 2 of the major trials (119,120).

c. Interventions to be Considered for Use in Selected Patients

ISOSORBIDE DINITRATE

Isosorbide dinitrate was one of the first vasodilator agents reported to be useful for chronic therapy of HF. Nitrate therapy may decrease symptoms of dyspnea at night and during exercise and may improve exercise tolerance in patients who have persistent limitation despite optimization of other therapies (125).

The only common side effects of nitrate therapy are headaches and hypotension. In clinical use, nitrates are frequently prescribed to patients with persistent congestive symptoms. Although the only large trial of nitrates in HF (125a) used a combination of nitrates and hydralazine, nitrates predominantly are potent venodilators that also have effects on arterial tone when used alone, particularly when systemic vascular resistance is severely elevated. Because they act through cyclic guanosine monophosphate, there is a theoretical reason that they may be titrated up to facilitate weaning of intravenous infusions that act through the same pathway.

HYDRALAZINE

There are limited data regarding the use of hydralazine alone in HF.

HYDRALAZINE AND ISOSORBIDE DINITRATE

A post hoc retrospective analysis of 2 vasodilator trials demonstrated particular efficacy of isosorbide dinitrate and hydralazine in the black cohort (125b). A confirmatory trial has been done. In that trial, which was limited to the black population with HF, the addition of hydralazine and isosorbide dinitrate to therapy with an ACEI and/or a beta-blocker was shown to be of significant benefit (160). The benefit was presumed to be related to enhanced nitric oxide bioavailability. Whether this benefit is evident in other patients with HF remains to be investigated. The combination of hydralazine and isosorbide dinitrate should not be used for the

treatment of HF in patients who have no prior use of an ACEI and should not be substituted for ACEIs in patients who are tolerating ACEIs without difficulty.

Despite the lack of data with the vasodilator combination in patients who are intolerant of ACEIs, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients. However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions (70,127). For patients with more severe symptoms and ACEI intolerance, the combination of hydralazine and nitrates is used frequently, particularly when ACEI therapy is limited by hypotension or renal insufficiency. There are, however, no trials addressing the use of isosorbide dinitrate and hydralazine specifically in the population of patients who have persistent symptoms and intolerance to inhibitors of the renin-angiotensin system.

CARDIAC RESYNCHRONIZATION THERAPY

To date, more than 4000 HF patients with ventricular dyssynchrony have been evaluated in randomized controlled trials of optimal medical therapy alone versus optimal medical therapy plus cardiac resynchronization therapy with or without an ICD. Cardiac resynchronization therapy, when added to optimal medical therapy in persistently symptomatic patients, has resulted in significant improvements in quality of life, functional class, exercise capacity, exercise distance, EF, and survival in patients randomized to such therapy (128) or to the combination of cardiac resynchronization therapy and ICD (129-131). The use of an ICD in combination with cardiac resynchronization therapy should be based on the indications for ICD therapy. Recommendations regarding cardiac resynchronization therapy for patients with right bundle-branch block, atrial fibrillation, minor conduction abnormality, and pacemaker dependence as well as inadequate medical therapy must await the completion of ongoing or future trials.

d. Drugs and Interventions Under Active Investigation

Several drugs that showed promise in pilot studies and were included in this section in the 2001 guidelines failed to live up to their promise in long-term, large-scale trials and are no longer included as "promising" in this update. Several remain under or have begun active investigation. Investigational drug therapies currently in phase III evaluation for the treatment of chronic HF include vasopressin receptor antagonists, intermittent nesiritide infusions, and oral phosphodiesterase III inhibitors. In addition, newer devices and technologies, such as implantable hemodynamic monitors and internal cardiac support devices, external counterpulsation, treatment for sleep-disordered breathing, myocardial growth factors and stem cell transplantation, and devices to achieve intravascular volume reduction, as well as novel surgical approaches, including surgical ventricular restoration, are under active investigation.

e. Drugs and Interventions of Unproved Value and Not Recommended

NUTRITIONAL SUPPLEMENTS AND HORMONAL THERAPIES

Aside from replenishment of documented deficiencies, randomized trials have failed to demonstrate benefit for routine vitamin supplementation (132). No clinical trials have demonstrated improved survival in users of nutritional or hormonal therapy.

TABLE 7. Recommendations for Treatment of Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

Recommendation	Class	Level of Evidence
Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.	I	A
Physicians should control ventricular rate in patients with atrial fibrillation.	I	C
Physicians should use diuretics to control pulmonary congestion and peripheral edema.	I	C
Coronary revascularization is reasonable in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.	IIb	C
The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.	IIb	C
The use of digitalis to minimize symptoms of heart failure is not well established.	IIb	C

2. Patients With HF and Normal LVEF

RECOMMENDATIONS

CLASS I

1. Physicians should control systolic and diastolic hypertension in patients with HF and normal LVEF, in accordance with published guidelines. (*Level of Evidence: A*)
2. Physicians should control ventricular rate in patients with HF and normal LVEF and atrial fibrillation. (*Level of Evidence: C*)
3. Physicians should use diuretics to control pulmonary congestion and peripheral edema in patients with HF and normal LVEF. (*Level of Evidence: C*)

CLASS IIa

1. Coronary revascularization is reasonable in patients with HF and normal LVEF and coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function. (*Level of Evidence: C*)

CLASS IIb

1. Restoration **and maintenance of** sinus rhythm in patients with atrial fibrillation and HF and normal LVEF might be useful **to improve symptoms**. (*Level of Evidence: C*)
2. The use of beta-adrenergic blocking agents, ACEIs, ARBs, or calcium antagonists in patients with HF and normal LVEF and controlled hypertension might be effective to minimize symptoms of HF. (*Level of Evidence: C*)
3. The usefulness of digitalis to minimize symptoms of HF in patients with HF and normal LVEF is not well established. (*Level of Evidence: C*)

TABLE 8. Differential Diagnosis in a Patient With Heart Failure and Normal Left Ventricular Ejection Fraction

Incorrect diagnosis of HF
Inaccurate measurement of LVEF
Primary valvular disease
Restrictive (infiltrative) cardiomyopathies
Amyloidosis, sarcoidosis, hemochromatosis
Pericardial constriction
Episodic or reversible LV systolic dysfunction
Severe hypertension, myocardial ischemia
HF associated with high metabolic demand (high-output states)
Anemia, thyrotoxicosis, arteriovenous fistulae
Chronic pulmonary disease with right HF
Pulmonary hypertension associated with pulmonary vascular disorders
Atrial myxoma
Diastolic dysfunction of uncertain origin
Obesity
HF indicates heart failure; LV, left ventricular; and LVEF, left ventricular ejection fraction.

Table 7 summarizes the recommendations for treatment of patients with HF and normal LVEF.

a. Identification of Patients

Over the past few years, there has been a growing appreciation that a large number of patients with HF have a relatively normal EF, or preserved EF. The pathophysiology of this type of HF has been reviewed in depth (133), and a large, randomized study that enrolled patients with HF and normal EF has been completed (134). Heart failure associated with relatively preserved LVEF is most prevalent among elderly women, most of whom have hypertension, diabetes mellitus, or both and often coronary artery disease or atrial fibrillation as well (135).

A number of recent investigations have focused on the differences between HF with preserved EF and that with low LVEF (135a,136). Myocardial infarction or other evidence of atherosclerotic disease appears to be less common in HF with normal LVEF, but hypertension is at least as common in this subgroup. The morbidity and mortality associated with HF and a relatively preserved LVEF may be nearly as profound as that with low LVEF; frequent and repeated hospitalizations characterize the patient with HF and a normal LVEF (137,138). Most, but not all, series of patients with HF and relatively preserved LVEF have shown better survival than is seen in patients with HF and reduced LVEF; however, these comparisons are difficult to interpret, because it is difficult to be certain that such series do not contain at least some patients in whom the diagnosis of HF is erroneous.

b. Diagnosis

There have been several proposed criteria by which clinicians and investigators may define HF with a relatively preserved LVEF (139–142). In general, a definitive diagnosis can be made when the rate of ventricular relaxation is slowed; this physiological abnormality is characteristically associated with the finding of an elevated LV

filling pressure in a patient with normal LV volumes and contractility. In practice, the diagnosis is generally based on the finding of typical symptoms and signs of HF in a patient who is shown to have a normal LVEF and no valvular abnormalities (aortic stenosis or mitral regurgitation, for example) on echocardiography. Every effort should be made to exclude other possible explanations or disorders that may present in a similar manner (144,145) (Table 8).

c. Principles of Treatment

In the absence of controlled clinical trials, the management of these patients with HF and preserved LVEF is based on the control of physiological factors (blood pressure, heart rate, blood volume, and myocardial ischemia) that are known to exert important effects on ventricular relaxation (144). Likewise, diseases that are known to cause HF with normal LVEF should be treated, such as coronary artery disease, hypertensive heart disease, or aortic stenosis. Clinically, it seems reasonable to target symptom reduction, principally by reducing cardiac filling pressures at rest and during exertion (133).

D. Patients With Refractory End-Stage HF (Stage D)

RECOMMENDATIONS

CLASS I

1. Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF. (Level of Evidence: B)
2. Referral for cardiac transplantation in **potentially** eligible patients is recommended for patients with refractory end-stage HF. (Level of Evidence: B)
3. Referral of patients with refractory end-stage HF to an HF program with expertise in the management of refractory HF is useful. (Level of Evidence: A)
4. **Options for end-of-life care should be discussed with the patient and family when severe symptoms in patients with refractory end-stage HF persist despite application of all recommended therapies.** (Level of Evidence: C)
5. **Patients with refractory end-stage HF and implantable defibrillators should receive information about the option to inactivate defibrillation.** (Level of Evidence: C)

CLASS IIA

1. **Consideration of an LV assist device as permanent or "destination" therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy.** (Level of Evidence: B)

CLASS IIB

1. Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory end-stage HF and persistently severe symptoms. (Level of Evidence: C)
2. The effectiveness of mitral valve repair or replacement is not established for severe secondary mitral regurgitation in refractory end-stage HF. (Level of Evidence: C)
3. Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in

TABLE 9. Indications for Cardiac Transplantation

Absolute indications in appropriate patients

- For hemodynamic compromise due to HF
 - Refractory cardiogenic shock
 - Documented dependence on IV inotropic support to maintain adequate organ perfusion
 - Peak Vo_2 less than 10 ml per kg per min with achievement of anaerobic metabolism
- Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention
- Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities

Relative indications

- Peak Vo_2 11 to 14 ml per kg per min (or 55% of predicted) and major limitation of the patient's daily activities
- Recurrent unstable ischemia not amenable to other intervention
- Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen

Insufficient indications

- Low left ventricular ejection fraction
- History of functional class III or IV symptoms of HF
- Peak Vo_2 greater than 15 ml per kg per min (and greater than 55% of predicted) without other indications

HF indicates heart failure; IV, intravenous; and Vo_2 , oxygen consumption per unit time.

patients with refractory end-stage HF. (Level of Evidence: C)

CLASS III

1. Partial left ventriculectomy is not recommended in patients with **nonischemic cardiomyopathy** and refractory end-stage HF. (Level of Evidence: C)
2. Routine intermittent infusions of positive inotropic agents are not recommended for patients with refractory end-stage HF. (Level of Evidence: B)

1. Management of Fluid Status

A critical step in the successful management of end-stage HF is the recognition and meticulous control of fluid retention.

2. Intravenous Peripheral Vasodilators and Positive Inotropic Agents

Patients who cannot be weaned from intravenous to oral therapy despite repeated attempts on multiple occasions may require the continuous infusion of dobutamine or milrinone, or as has been used more recently, nesiritide. Such a strategy is commonly used in patients who are awaiting cardiac transplantation, but it may also be used in the outpatient setting in patients who are not being considered for transplantation but who otherwise cannot be discharged from the hospital. The decision to continue intravenous infusions at home should not be made until all alternative attempts to achieve stability have failed repeatedly, because such an approach can present a major burden to the family and health services and may ultimately increase the risk of death.

However, continuous intravenous inotropic support can provide palliation of symptoms as part of an overall plan to allow the patient to die with comfort at home (146,147). The use of continuous intravenous inotropic support to allow hospital discharge should be distinguished from the intermittent administration of infusions of such positive inotropic agents to patients who have been successfully weaned from inotropic support.

3. Mechanical and Surgical Strategies

Cardiac transplantation is currently the only established surgical approach to the treatment of refractory HF, but it is available to fewer than 2500 patients in the United States each year (148,149). Current indications for cardiac transplantation focus on the identification of patients with severe functional impairment or dependence on intravenous inotropic agents (Table 9). Alternate surgical and mechanical approaches for the treatment of end-stage HF are under development. Hemodynamic and clinical improvement has been reported after mitral valve repair or replacement in patients who have a clinically important degree of mitral regurgitation that is secondary to LV dilatation (150). However, no controlled studies have evaluated the effects of this procedure on ventricular function, clinical status, or survival.

A variant of the aneurysmectomy procedure is now being developed for the management of patients with ischemic cardiomyopathy (151), but its role in the management of HF remains to be defined. None of the current surgical reconstruction techniques offer “rescue therapy” to patients with critical hemodynamic compromise. The use of mechanical circulatory assist devices in end-stage HF is an area of intense investigation. A recent trial provided evidence that non-transplant-eligible patients requiring continuous intravenous inotropic infusions could derive benefit from permanent implantation of an LV device.

V. Treatment of Special Populations

RECOMMENDATIONS

CLASS I

1. Groups of patients including (a) high-risk ethnic minority groups (e.g., blacks), (b) groups underrepresented in clinical trials, and (c) any groups believed to be underserved should, in the absence of specific evidence to direct otherwise, have clinical screening and therapy in a manner identical to that applied to the broader population. (*Level of Evidence: B*)
2. It is recommended that evidence-based therapy for HF be used in the elderly patient, with individualized consideration of the elderly patient's altered ability to metabolize or tolerate standard medications. (*Level of Evidence: C*)

CLASS IIA

1. The addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs and beta-blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested. (*Level of Evidence: A*)

Many patients with HF are members of subpopulations who are likely to exhibit unique responses that accelerate the development or progression of HF or complicate the management of HF.

A. Women and Men

Most large, multicenter trials have not included sufficient numbers of women to allow conclusions about the efficacy and safety of their treatment. The conflicting data regarding the efficacy of digoxin in women suggests that if it is prescribed, particular attention should be paid to dosing and renal function.

B. Ethnic Considerations

Race is an imprecise concept that has largely become a social and political construct with more limited biological significance (152). The concept of racial “minorities” may be relevant to large populations, especially those in clinical trials, but is clearly not a concept applicable in many demographic areas and clinical practices. However, it is useful to review epidemiological and clinical trial evidence to raise awareness of potential areas of concern and guide socioeconomic and clinical remedies. Heart failure has a 50% higher incidence in the black population than is seen in the general population. Deficiencies in cardiovascular risk factor and disease detection and treatment as well as in access to quality outpatient care may contribute to the increased incidence and morbidity of blacks with HF (153–155). Blacks and other racial minorities with HF are underrepresented in most clinical trials of new drugs for HF, which compromises the extrapolation of results from major clinical trials to ethnic subgroups.

The emerging field of genomic medicine has begun to suggest that important variances in the expression of certain high-risk, single-nucleotide polymorphisms may be evident along racial lines and may provide a physiological basis for differences in the natural history of HF and differences in drug responsiveness (156–159). Data from these early investigations are not yet definitive; racial groupings are necessarily heterogeneous, and data will need to be interpreted cautiously.

A prospective, double-blind, randomized trial conducted specifically in blacks with NYHA class III/IV HF has been completed. In this trial, the adjunctive use of a proprietary formulation of isosorbide dinitrate and hydralazine along with a standard HF regimen resulted in a 43% decrease in total mortality, which led to premature termination of the trial. Additionally, time to first hospitalization and quality of life were both improved (160).

C. Elderly Patients

The prevalence of HF rises from 2% to 3% at age 65 to more than 80% in persons over 80 years of age. Heart failure in elderly patients is inadequately recognized and treated (161). Both patients and physicians frequently attribute the symptoms of HF to aging, and noninvasive cardiac imaging commonly fails to reveal impaired systolic function because HF with a preserved LVEF is frequently found in the elderly.

VI. Patients With HF Who Have Concomitant Disorders

RECOMMENDATIONS

CLASS I

1. **All other recommendations should apply to patients with concomitant disorders unless there are specific exceptions. (Level of Evidence C)**
2. Physicians should control systolic and diastolic hypertension **and diabetes mellitus** in patients with HF in accordance with recommended guidelines. (Level of Evidence: C)
3. Physicians should use nitrates and beta-blockers for the treatment of angina in patients with HF. (Level of Evidence: B)
4. Physicians should recommend coronary revascularization **according to recommended guidelines** in patients who have both HF and angina. (Level of Evidence: A)
5. Physicians should prescribe anticoagulants in patients with HF who have paroxysmal or **persistent** atrial fibrillation or a previous thromboembolic event. (Level of Evidence: A)
6. Physicians should control the ventricular response rate in patients with HF and atrial fibrillation with a beta-blocker (or amiodarone, if the beta-blocker is contraindicated or not tolerated). (Level of Evidence: A)
7. **Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina. (Level of Evidence: C)**
8. **Physicians should prescribe antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease. (Level of Evidence: B)**

CLASS IIA

1. It is reasonable to prescribe digitalis to control the ventricular response rate in patients with HF and atrial fibrillation. (Level of Evidence: A)
2. **It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias (Level of Evidence: C)**

CLASS IIB

1. The usefulness of **current strategies to restore and maintain** sinus rhythm in patients with HF and atrial fibrillation is not well established. (Level of Evidence: C)
2. The usefulness of anticoagulation is not well established in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. (Level of Evidence: B)
3. **The benefit of enhancing erythropoiesis in patients with HF and anemia is not established. (Level of Evidence C)**

CLASS III

1. Class I or III antiarrhythmic drugs are not recommended in patients with HF for the prevention of ventricular arrhythmias. (Level of Evidence: A)
2. **The use of antiarrhythmic medication is not indicated as primary treatment for asymptomatic ventricular arrhythmias or to improve survival in patients with HF. (Level of Evidence: A)**

A. Cardiovascular Disorders

1. Hypertension, Hyperlipidemia, and Diabetes Mellitus

Heart failure may complicate the management of both hypertension and diabetes mellitus. Some antihypertensive agents should be avoided in patients with HF because of their ability to depress cardiac function or to lead to salt and water retention. Thiazolidinediones have been associated with increased peripheral edema and symptomatic HF in patients with underlying risk factors or known cardiovascular disease. The risk of developing edema with thiazolidinediones is dose related and is higher in diabetic patients who are taking concomitant insulin therapy. However, the incidence of thiazolidinedione-related fluid retention is low in patients with NYHA functional class I to II symptoms, in whom these drugs can be administered safely with careful monitoring for fluid retention. Initiation of these drugs is not recommended in patients with NYHA functional class III to IV symptoms of HF (162).

2. Supraventricular Arrhythmias

Supraventricular tachyarrhythmias may exert adverse effects by 4 different mechanisms: 1) the loss of atrial enhancement of ventricular filling may compromise cardiac output; 2) the rapid heart rate may increase demand and decrease coronary perfusion (by shortening ventricular filling time); 3) the rapidity of ventricular response may diminish both cardiac contraction (by aggravating abnormalities of the force-frequency relation) (163,164) and cardiac relaxation (165,166); and 4) the stasis of blood in the fibrillating atria may predispose patients to pulmonary or systemic emboli. Specific care and initially low doses should be used when instituting beta-blockers to control heart rate in patients with clinical evidence of HF decompensation.

The efficacy and safety of restoring and maintaining sinus rhythm in patients with atrial fibrillation was recently evaluated in 4 separate trials (167). These trials consistently showed no improvement in mortality or morbidity using a strategy of aggressive rhythm control. However, the rate-control strategy was associated with fewer hospitalizations and fewer side effects from drug therapy. Until more definitive data are available, treatment must be individualized.

3. Prevention of Thromboembolic Events

A randomized trial comparing the outcome of patients with HF and low EF assigned to aspirin, warfarin, or clopidogrel was completed recently. Unfortunately, low enrollment in the trial precluded definitive conclusions about efficacy, but no therapy appeared to be superior. Another trial is currently under way comparing aspirin with warfarin in patients with reduced LVEF and may provide more definitive data upon which to base recommendations.

B. Noncardiovascular Disorders

1. Patients With Pulmonary Disease

Some drugs used to treat HF can produce or exacerbate pulmonary symptoms. ACEIs can cause a persistent nonproductive cough that can be confused with a respiratory infection, and conversely, ACEIs may be inappropriately stopped in patients with pulmonary causes of cough. Therefore, physicians

should seek a pulmonary cause in all patients with HF who complain of cough, whether or not they are taking an ACEI. Because the ACEI-related cough does not represent any serious pathology, many patients can be encouraged to tolerate it in view of the important beneficial effects of ACEI. Beta-blockers can aggravate bronchospastic symptoms in patients with asthma; however, many patients with asymptomatic or mild reactive airway disease tolerate beta-blockers well.

2. Patients With Cancer

Heart failure may appear many years after anthracycline exposure, particularly in association with another stress, such as tachycardia. Although once thought to progress inexorably, HF related to chemotherapy often improves in response to therapy, even when it appears late after exposure.

3. Patients With Thyroid Disease

Special vigilance is required for patients taking amiodarone, who may develop either hyperthyroidism or hypothyroidism. New atrial fibrillation or exacerbation of ventricular arrhythmias should trigger re-evaluation of thyroid status.

4. Patients With Hepatitis C and Human Immunodeficiency Virus

Hepatitis C viral infection can be a cause of cardiomyopathy and myocarditis. A small study showed that hepatitis C virus myocarditis might respond favorably to immunosuppressive therapy with prednisone and azathioprine (168,169). Preliminary data also suggest that hepatitis C virus myocarditis might respond well to interferon therapy (170), although there is concern that interferon can also depress myocardial function.

Human immunodeficiency virus has been recognized as a probable occasional cause of dilated cardiomyopathy. Because of the occurrence of complex opportunistic infections, autoimmune responses to the viral infection, and drug cardiotoxicity, it is difficult to determine how therapies influence the development and control of cardiomyopathy with human immunodeficiency virus (171).

5. Patients With Anemia

Patients with HF frequently have anemia for a variety of reasons. The severity of anemia may contribute to the increasing severity of HF. Several studies have demonstrated worse patient outcomes in patients with HF and anemia (172,173). It is unclear whether anemia is the cause of decreased survival or a result of more severe disease.

VII. End-of Life Considerations

RECOMMENDATIONS

CLASS I

1. Ongoing patient and family education regarding prognosis for functional capacity and survival is recommended for patients with HF at the end of life. (*Level of Evidence: C*)
2. Patient and family education about options for formulating

and implementing advance directives **and the role of palliative and hospice care services with re-evaluation for changing clinical status** is recommended for patients with HF at the end of life. (*Level of Evidence: C*)

3. **Discussion is recommended regarding the option of inactivating ICDs for patients with HF at the end of life.** (*Level of Evidence: C*)
4. It is important to ensure continuity of medical care between inpatient and outpatient settings for patients with HF at the end of life. (*Level of Evidence: C*)
5. Components of hospice care that are appropriate to the relief of suffering, **including opiates**, are recommended **and do not preclude the options for use of inotropes and intravenous diuretics for symptom palliation** for patients with HF at the end of life. (*Level of Evidence: C*)
6. **All professionals working with HF patients should examine current end-of-life processes and work toward improvement in approaches to palliation and end-of-life care.** (*Level of Evidence: C*)

CLASS III

1. **Aggressive procedures performed within the final days of life (including intubation and implantation of a cardioverter-defibrillator in patients with NYHA functional class IV symptoms who are not anticipated to experience clinical improvement from available treatments)** are not appropriate. (*Level of Evidence: C*)

The patient should be encouraged to choose in advance a person to assume legal authority (i.e., designated power of attorney or healthcare proxy) for healthcare matters when the patient cannot be involved in decisions. That individual should serve as the contact point for the team. Professionals caring for patients with advanced HF should have realistic expectations for survival and communicate those accurately to patients and families. Also, the professionals should provide realistic recommendations for procedures being done within the final days of life that do not add to the hope of recovery or improvement in life quality. Finally, greater attention and research need to be devoted to the provision of comfort measures in the final days of life, including relief of pain and dyspnea.

Ultimately, the decisions regarding when end of life is nearing reflect a complex interaction between objective information and subjective information, emotions, and patient and family readiness. Ideally, these decisions would be made in conjunction with the individual or team most experienced in caring for advanced HF or in collaboration and/or consultation with such an expert. In reality, however, this does not occur often. The Writing Committee recommends that all those involved with HF care make it a priority to improve recognition of end-stage disease and provide care to patients and families approaching this stage. As we become more familiar with the steps in progression to end-stage HF in this era, the current abrupt transition from aggressive intervention to comfort and bereavement care will be softened by a gradual and progressive emphasis on palliation until it dominates the final days of care (174).

VIII. Implementation of Practice Guidelines

RECOMMENDATIONS

CLASS I

1. Academic detailing or educational outreach visits are useful to facilitate the implementation of practice guidelines. (*Level of Evidence: A*)
2. Multidisciplinary disease-management programs for patients at high risk for hospital admission or clinical deterioration are recommended to facilitate the implementation of practice guidelines, **attack different barriers to behavioral change, and reduce the risk of subsequent hospitalization for HF.** (*Level of Evidence: A*)

CLASS IIA

1. Chart audit and feedback of results can be effective to facilitate implementation of practice guidelines. (*Level of Evidence: A*)
2. The use of reminder systems can be effective to facilitate implementation of practice guidelines. (*Level of Evidence: A*)
3. **The use of performance measures based on practice guidelines may be useful to improve quality of care.** (*Level of Evidence: B*)
4. **Statements by and support of local opinion leaders** can be helpful to facilitate implementation of practice guidelines. (*Level of Evidence: A*)

CLASS IIB

1. Multidisciplinary disease-management programs for patients at low risk for hospital admission or clinical deterioration may be considered to facilitate implementation of practice guidelines. (*Level of Evidence: B*)

CLASS III

1. Dissemination of guidelines without more intensive behavioral change efforts is not useful to facilitate implementation of practice guidelines. (*Level of Evidence: A*)
2. Basic provider education alone is not useful to facilitate implementation of practice guidelines. (*Level of Evidence: A*)

Performance Measures

Performance measures are standards of care for a particular illness or condition that are designed to assess and subsequently improve the quality of medical care and are chosen on the basis of the knowledge or assumption that the particular item is linked to improved patient outcomes. The ACC and AHA are collaborating with a variety of organizations to develop and implement performance measures.

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